

the German literature in 1953 and 1954,^{16,17} and in 1960 Keal¹⁸ reported the association of peritoneal mesotheliomas and asbestos exposure. Also in 1960 Wagner et al.¹⁹ reported 33 cases of diffuse pleural mesothelioma in the North Western Cape Province of South Africa. Of these 33 patients, 32 had exposure to asbestos. Wagner^{20,21} recounted his experience with the discovery of mesotheliomas in South Africa, and further suggested that all pleural mesotheliomas in the United States were caused by crocidolite asbestos, a suggestion with which we strongly disagree and which is not supported in the medical literature.^{22,23} Smither et al.²⁴ and McCaughey et al.²⁵ recorded additional cases of asbestos-related mesothelioma in 1962, and for some of those cases the exposure appeared to have been minimal. In the same year, Wagner et al.^{26,27} published studies on the mucin histochemistry of mesothelioma and on the induction of malignant mesothelioma (MM) in experimental animals by asbestos.

In 1964 and 1965 Selikoff and colleagues^{28,29} linked mesotheliomas to asbestos exposure by finding that 10 of 307 consecutive deaths in asbestos insulation workers were caused by diffuse mesothelioma. Also in 1965 Newhouse and Thompson^{30,31} recorded the occurrence of mesotheliomas as a consequence of domestic (household contact) asbestos exposure among those who shook out and laundered the asbestos-contaminated work clothes of their partners, and from neighborhood exposure acquired by residence in the vicinity of an asbestos factory. Most MMs reported since 1970 have been diffuse; the localized form is rare.^{18,32}

By the late 1990s, the incidence of MM in some industrialized nations was comparable to that of cancer of the larynx,³³ with a death rate similar to that of renal cell carcinoma in males and uterine cancer in females.³³⁻³⁷ Apart from lung cancer,³⁸ MM is now the most important occupational cancer among industrial workers, because of its prevalence, resistance to conventional cancer treatments, and its lethality.

The history of the medical-legal aspects of asbestos-related lung disease was discussed in detail by Motley³⁹ and Brodeur.^{40,41} Information presented by these authors suggested that serious deleterious health effects of asbestos were known long before they were reported in the medical literature.

Incidence and Epidemiology

Mesotheliomas encountered in the early 21st century are most often a consequence of prior occupational exposure to asbestos from the 1940s through the 1970s, including end-uses of asbestos-containing materials and "bystander" (indirect) exposures.^{36,42-44} The relationship between inhalation of asbestos fibers—especially one or more of the amphibole varieties—and MM is accepted by virtually all authorities as causal.⁴² Because of the constancy and specificity of the asbestos-MM relationship, the incidence of mesothelioma is usually considered to reflect a society's past per capita usage of asbestos,⁴⁵⁻⁴⁸ after allowance for a suitable latency interval between first exposure to asbestos and the subsequent rise in incidence of MM (Fig. 43.1 and Table 43.1).^{47,49}

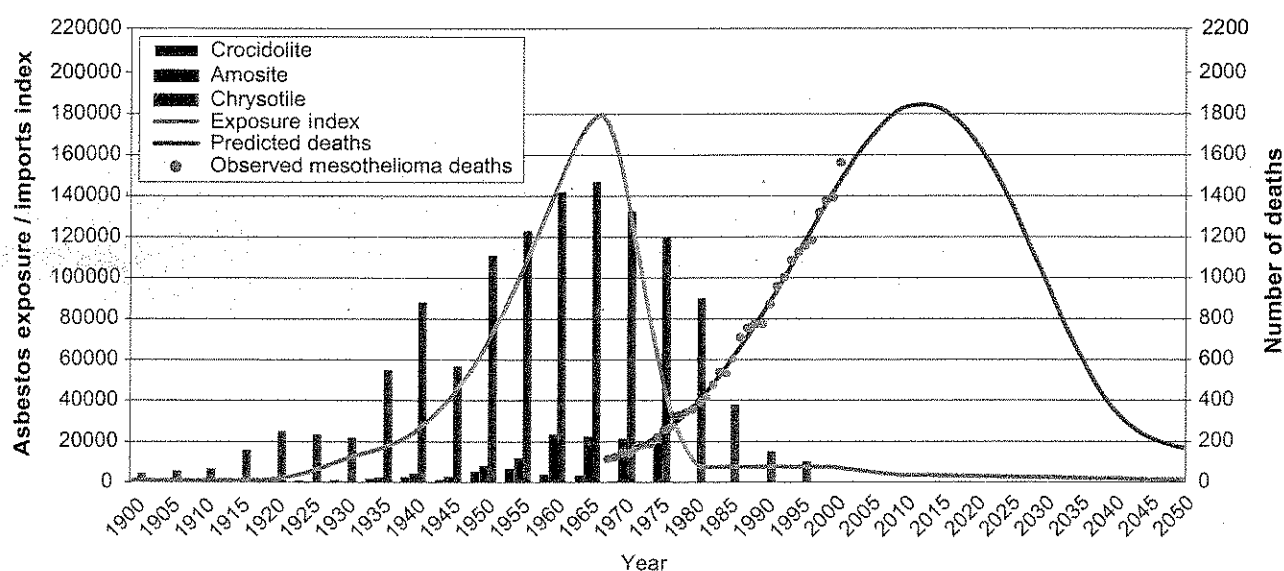


FIGURE 43.1. Observed and predicted deaths from mesothelioma in the United Kingdom, versus asbestos imports and estimated exposure indices, for men aged 20 to 89, for the years

1900 to 2050. (Modified from Health and Safety Executive [HSE]. Mesothelioma mortality in Great Britain: estimating the future burden, December 2003, with permission of the HSE.)

TABLE 43.1. Mesothelioma incidence for some countries relative to their historical per capita use of asbestos

Country	Mesothelioma incidence cases/10 ⁶ /yr	Use of asbestos in kg/capita (year)
Australia (1995)	33	4.4 (1968)
Netherlands (1995)	27	3.4 (1976)
United Kingdom (1991)	23	2.7 (1970)
Italy (1993)	22	2.5 (1975)
France (1996)	17	2.6 (1970)
Finland (1995)	15	2.2 (1970)
Germany (1997)	15	3.0 (1975)
Sweden (1995)	15	2.4 (1970)
United States (2000)	15	2.3 (1975)
Norway (1995)	14	1.9 (1970)

Source: Modified from Tossavainen.⁴⁷

Because mesotheliomas are rare neoplasms, their exact incidence is unknown and varies among populations surveyed (Table 43.2).⁵⁰⁻⁵⁹ The highest incidence in the world is currently in Australia.⁵⁸

The incidence of mesothelioma in autopsy series is considerably lower. McDonald and McDonald⁵⁹ summarized the incidence in six series from eight cities between 1950 and 1970. They tabulated 165 cases in 69,302 autopsies (0.24%).

Several studies^{54,56,57} documented an apparent increased incidence of MM, especially in men, during the last several decades. Hughes and Weill⁶⁰ estimated that 1500 new cases of mesothelioma were diagnosed in the United States in 1986. The increased incidence of MM is probably related to the delayed effects of an increase in occupational exposure to asbestos. Selikoff et al.²⁸ reported that 8% of 17,800 workers in the heat and frost insulation

industry who were followed prospectively between January 1, 1967, and December 31, 1976, died of diffuse MM.⁶¹ According to Huncharek,⁶² the incidence of mesothelioma is increasing at a rate of about 10% per year for U.S. males.

The authors' experience has also suggested an increased incidence of MM that, in part, may reflect an increased awareness by pathologists of mesothelioma and of more accurate diagnostic methods such as electron microscopy and immunohistochemistry. In addition, many cases of mesothelioma in the United States come to litigation, which has made the general public more aware of mesothelioma and, in turn, has caused heightened physician awareness.

According to the Environmental Working Group,⁶³ there is an asbestos epidemic in America. This group reports that asbestos-related disease is responsible for the death of one in 125 American men over the age of 50, and that 10,000 Americans die each year—30 per day—from asbestos-caused diseases. At this time, the death toll is rising in nine of the 10 states with the highest number of mesotheliomas and asbestosis deaths. Between 1979 and 2001, more than 43,000 Americans died from MM. According to Price,⁶⁴ there are approximately 2500 new cases of MM annually in the U.S., 80% of which occur in men.⁶⁵ According to Price, the incidence of mesothelioma appears to be rising in men aged 45 years or older, with a maximum lifetime risk in the 1925 to 1929 cohort. The incidence of MM in women and in men less than 75 years of age is claimed to have been stable since 1983⁶⁴ (but see later discussion).

Peto et al.⁶⁶ predicted MM deaths would continue to increase for at least 15, and more likely 25, years. In the most affected cohort, men born in the 1940s, MM would

TABLE 43.2. Incidence of mesotheliomas^a

Reference	Years surveyed	Location of population surveyed	Number of cases/million population/year
McDonald et al. ⁵⁰	1959-mid-1968	Canada	0.65 (males) 0.35 (females)
Theriault and Grand-Bois ⁵¹	1969-1972	Quebec	1.56 (males) 0.74 (females)
Biava et al. ⁵²		Italy	21.4 (males)
Greenberg and Lloyd-Davies ⁵³	1967-1968	England, Wales, Scotland	1.88 (males) 0.42 (females)
McDonald and McDonald ⁵⁴	1960-1975	Canada	2.8 (males)
	1972	United States	0.7 (females)
Cutler and Young ⁵⁵	1969-1971	Metropolitan area ^b	1.5 (males) 0.7 (females)
Bruckman et al. ⁵⁶	1970-1972	Connecticut (U.S.)	1.7 (males) 0.9 (females)
Churg ⁵⁷	1982	British Columbia	17 (males) 1.9 (females)
McDonald and McDonald ⁵⁹	1950-1970	Eight cities	0.24% of 69,302 autopsies

^aIncidence includes both pleural and peritoneal mesotheliomas, and in some instances mesotheliomas arising in ovary and male genital system.

^bAtlanta, Birmingham, Dallas-Ft. Worth, Detroit, Pittsburgh, San Francisco-Oakland, Denver (U.S.).

account for around 1% of all deaths. In 2005 Hodgson et al.⁶⁷ stated there were 1848 mesothelioma deaths in Great Britain in 2001 and mesothelioma deaths were predicted to peak at around 1950 to 2450 per year between the years 2011 and 2015 (Fig. 43.1). The Health and Safety Executive Data⁶⁸ suggested the peak would occur earlier than originally predicted and the maximum would be approximately 2000 deaths in or around the year 2010. According to Treasure et al.,⁶⁹

one in every 100 men born in the 1940s will die of malignant pleural mesothelioma. . . . For a man first exposed as a teenager, who remained in a high-risk occupation such as insulation throughout his working life, the lifetime risk of mesothelioma can be as high as 1 in 5. . . . The disease is increasing in frequency. . . . We will see many more mesotheliomas in the next 25 years. In the developed world alone, 100,000 people alive will now die from it.

In Australia, mortality from MM was stated to have been increasing since 1975. Mesothelioma incidence rates are among the highest in the world, and the Australian Mesothelioma Registry received 6129 mesothelioma notifications between 1986 and 2000. Of the mesothelioma cases with past asbestos exposure, close to 89% were

work-related, about 3% were not work-related, and about 8% could not be classified. Of the persons who developed work-related MM, one in three worked in the construction industry and one in five worked in the manufacturing industry.

In contrast, Roggli,⁷⁰ based on his experience, suggests that a mesothelioma epidemic was beginning to wane in the U.S. Lemen,⁷¹ using Surveillance Epidemiology and End Results (SEER) data and International Classification of Diseases (ICD-10-TEM) coding that went into effect in 1999, stated the accuracy for reporting mesothelioma was about 80% effective, which would mean that in the U.S. there were over 6000 cases of mesothelioma per year.

Etiology

Asbestos

The association of asbestos exposure and the development of mesothelioma has been reviewed in detail.⁷²⁻⁷⁴ The chronology of asbestos is shown in Box 43.1 (Figs. 43.2 and 43.3). Asbestos is the single most important causative agent of mesothelioma. Numerous

Box 43.1. The History of Asbestos

4000 BCE	Asbestos was used for wicks in lamps and candles. "Asbestos" means inextinguishable or unquenchable.
2000–3000 BCE	Embalmed bodies of Egyptian pharaohs were wrapped in asbestos cloths to offset the ravages of time.
2500 BCE	Used in Finland to strengthen clay pots.
800–900 AD	Anecdotal evidence of Charlemagne's tablecloth made from woven asbestos.
1000	Mediterranean people used chrysotile from Cyprus and tremolite from upper Italy for the fabrication of cremation clothes, mats, and wicks for temple lamps.
1300–1400	Marco Polo visited an asbestos mine in China in the latter half of the 13th century. He concluded that asbestos was a stone and lay to rest the myth that asbestos was the hair of a woolly lizard.
Early 1700s	Asbestos papers and boards were made in Italy.
1724	Benjamin Franklin brought a purse made of asbestos to England. The purse is now in the Natural History Museum.
1828	United States patent issued for asbestos insulating material used in steam engines.
1853	Asbestos helmet and jackets worn by Parisian Fire Brigade.
1866	Molded lagging material made from water, glass, and asbestos.
1896	First asbestos brake linings were made by Ferodo Ltd., in England.
1900	High pressure asbestos gaskets made by Klinger in Austria.
1913	First asbestos pipes developed in Italy.
1919	Standard corrugated sheet asbestos introduced in Australia by Hardies.
1939–1945	Wartime use included fireproof suits and parachute flares. In the film <i>The Wizard of Oz</i> in 1939, the Wicked Witch of the West appeared on a broom made of asbestos.
1945–1975	Postwar construction projects relied heavily on the use of asbestos, reaching an all-time high in 1973.
1990s	The solid fuel boosters of the space shuttle are insulated with asbestos, one of the few remaining current uses.